J. Physiol. (1958) 141, 281–290

THE EFFECTS OF HEXAMETHONIUM BROMIDE ON TEMPERATURE REGULATION IN MAN

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(*Received* 25 *November* 1957)

The actions of autonomic blocking agents on temperature regulation of rats can be accounted for by the effects of increased heat loss subsequent to peripheral vasodilatation (Grayson & Mendel, 1956) and of reduced heat production due to blocking of 'chemical regulation' (Hsieh, Carlson & Gray, 1957). The latter effect is not important since 'chemical regulation' is significant only in cold-acclimatized rats and when muscle activity is blocked by curare (Cottle & Carlson, 1956). In man, increased skin temperature after sympathetic blockade with hexamethionium bromide has been reported (Finnerty & Freis, 1950). Hamilton, Henley & Morrison (1954) have suggested that increased heat loss from dilated vessels of the skin, mainly of the feet, may be responsible for the fall in body temperature following parenteral hexamethonium. The experiments of Hamilton *et al.* were performed on subjects comfortably warm. This paper reports experiments on two subjects, exposed to moderately low room temperature (20° C), in which oxygen consumption and regional skin temperatures were measured before and after intramuscular injection of hexamethonium bromide.

METHODS

The experiments were conducted before breakfast with the subjects lying nude in a room maintained at 20° C. The temperatures of the head, arms, hands, feet, legs, thighs and trunk were recorded by copper-constantan thermocouples taped to the skin and located at the points recommended by Hardy & DuBois (1938) whose formula was used for calculating the average skin temperature. Rectal temperature was recorded with a copper-constantan thermocouple probe inserted about 6 in. (15·2 cm). In calculating the mean body temperature the formula used was: mean body temp. $= 0{\cdot}65 \times$ (rectal temp.) $+ 0{\cdot}35 \times$ (average skin temp.) (Burton, 1935). Oxygen consumption was determined by measuring the inspiratory volume for 5 min periods and analysing samples of the expired air with a Pauling-Beckman oxygen-analyser (modified from Margaria, Meschia & Marro, 1954). Oxygen tension was read to the nearest 0·5 mm Hg.

Recordings were begun 30 min after the subject had removed his clothes and lain down on the bed. Four experimental procedures were followed: (*a*) control experiments in which the subjects lay quietly for 140 min; (*b*) after a control period of 50 min, 100 mg of hexamethonium bromide

(Vegolysen, May and Baker) was injected intramuscularly and the response followed for 90 min; (c) the effects on the response to hexamethonium produced by blocking the circulation to both feet for 20 min were tested by inflating to 260 mm Hg sphygmomanometer cuffs wrapped around the ankles; (d) the effects of reducing the heat loss from the feet on the response to hexamethonium were tested by keeping the feet wrapped in cotton-wool throughout the experimental period.

Each experiment was performed twice on the same subject. Tolerance to hexamethonium is assumed not to have occurred since the experiments were performed at intervals of at least 4 days.

RESULTS

Control experiments

With the subjects lying quietly at 20° C for 140 min a gradual fall of skin temperature occurred, most marked in the hands (6·3° C) and feet (7·4° C) and least in the head, trunk and thighs. The arms and legs showed an intermediate rate of fall, being about 4·6° and 2° C respectively during the period of recording (Fig. 1).

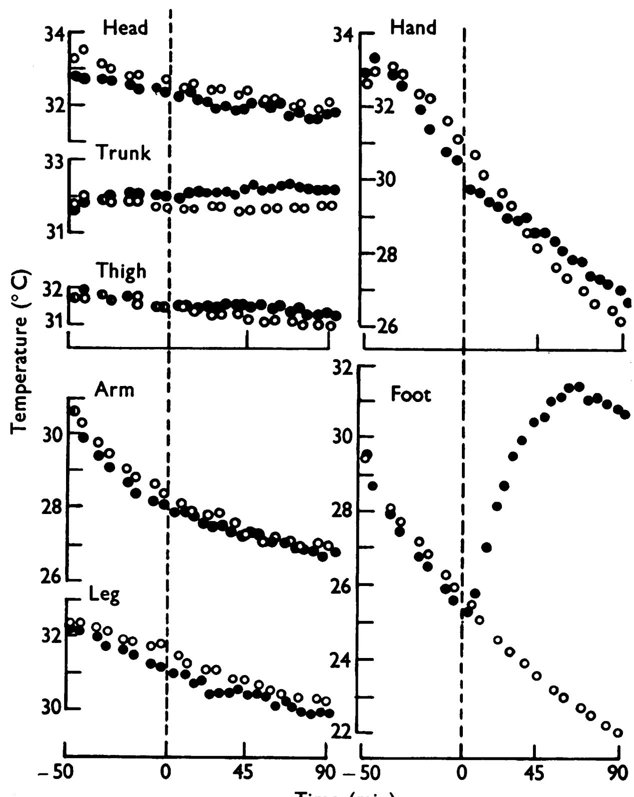

Fig. 1. Skin temperature of various regions of the body of nude subjects lying quietly at 20° C room temperature. ○, results from control experiments; ●, experiments in which 100 mg hexamethonium bromide was injected intramuscularly at zero time. Each point is the average of four experiments performed on two subjects.

The steady fall of foot temperature suggests that vasoconstriction was complete by the time recordings were begun. This assumption was tested in separate experiments in which cuffs wrapped around the ankles were inflated to 260 mm Hg for 15 min periods. Foot temperature continued to fall at the same rate during occlusion. After releasing the pressure in the cuffs a rise in temperature took place, coincidental with 'reactive hyperaemia', and reaching a maximum in 5 min; it then continued to fall at the previous rate (Fig. 2).

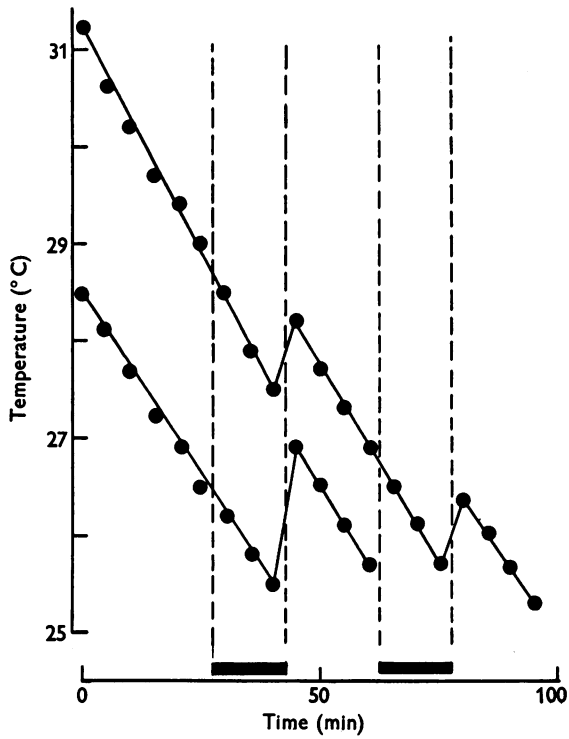

Fig. 2. The temperature of the feet of nude subjects lying quietly at 20° C room temperature. During the periods indicated by the horizontal bars, occlusion cuffs placed around the ankles were inflated to 260 mm Hg for 15 min.

Very little change in rectal temperature or in oxygen consumption took place during the test period (Fig. 3). During the last half hour of exposure the subjects experienced occasional muscle tremors over the trunk which were described as shivering. Assuming a caloric value of 4·82/l. O_2, the mean metabolic rate for the subjects was 36·2 kcal/m^2/hr.

The calculated average skin temperature was about 31·6° C at the beginning of the experiment and 29·7° C 140 min later (Fig. 4). When the temperatures of the hands and feet were omitted from the calculations the reduction in skin temperature was about 1° C. Thus the hands and feet, possessing only about

12% of the body surface area, were responsible for about 50% of the fall in the average skin temperature. The mean body temperature was 35·4° C at the beginning of the experiments and 34·6° C at the end.

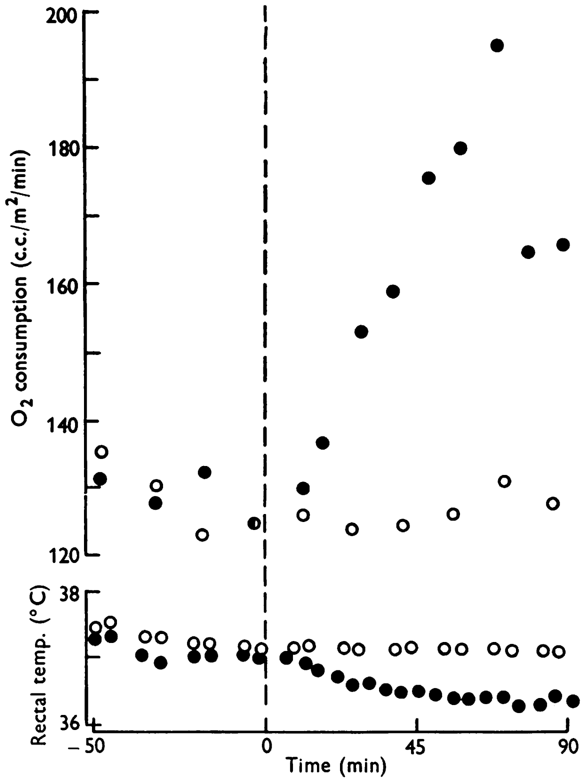

Fig. 3. Oxygen consumption and rectal temperatures obtained during the same experiments as in Fig. 1. The rise in oxygen consumption after the administration of hexamethonium is associated with shivering and follows the fall in rectal temperature.

Effects of hexamethonium

The temperature changes of the head, arms, legs and hands were not significantly altered after the injection of hexamethonium. Small increases in the temperature of the trunk and thighs were recorded, but as these were associated with vigorous shivering of the muscles in these areas it is possible that they were not due to direct action of the drug. The temperatures of the various regions are shown in Fig. 1, for comparison with the control readings.

The most striking change was the rise in the temperature of the feet. The response usually appeared within 5 min of the injection and reached a maximum in about 60 min. The maximum to which the temperature of the feet rose was fairly constant, being about 32·3° C. As the initial temperatures varied between 24·2° and 25·9° C, the magnitude of the rise was determined by the initial temperature of the feet. The average rise in foot temperature was about 5·7° C.

Soon after the temperature of the feet started to rise, the rectal temperature began to fall. The fall in rectal temperature was initially rapid, being about 0·5° C during the first 30 min after the injection. Thereafter, the rectal temperature remained at approximately the same level for the rest of the experimental period (Fig. 3).

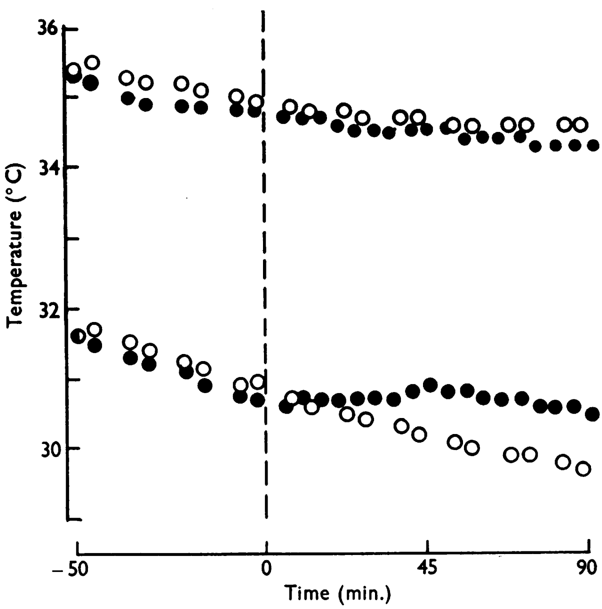

Fig. 4. Upper line, calculated mean body temperatures; lower line, average skin temperatures; obtained from the data for skin temperatures shown in Fig. 1, and rectal temperatures in Fig. 2. The mean body temperature is not altered by the injection of hexamethonium (upper solid circles).

The subjects began to shiver about 7 min after the injection of hexamethonium. Shivering started as occasional tremors of the intercostal muscles and became generalized in about 30 min. The occurrence of shivering was not associated with any feeling of coldness; on the contrary, the subjects felt warmer than before the injection of the drug. Oxygen consumption increased when shivering occurred, the increase being parallel to the vigour of the shivering (Fig. 3).

The calculated average skin temperature showed a slight rise above pre-injection levels, in contrast to the gradual fall observed in the control experiments. No significant difference was observed between the mean body temperature in the control experiments and those in which hexamethonium was injected (Fig. 4).

Effects of occlusion of blood flow to the feet

When the temperature of the feet began to show a reduced rate of fall, cuffs applied around the ankles were inflated to about 260 mm Hg for 20 min. During the period of occlusion there was no drop in rectal temperature and shivering did not occur. Release of the pressure in the cuffs was followed by a rapid fall in rectal temperature and shivering. Oxygen consumption, which was not elevated during the period of occlusion, rose sharply with the appearance of shivering (Fig. 5). Changes in the skin temperature of the head, trunk, thighs, arms, legs and hands were not altered by this procedure.

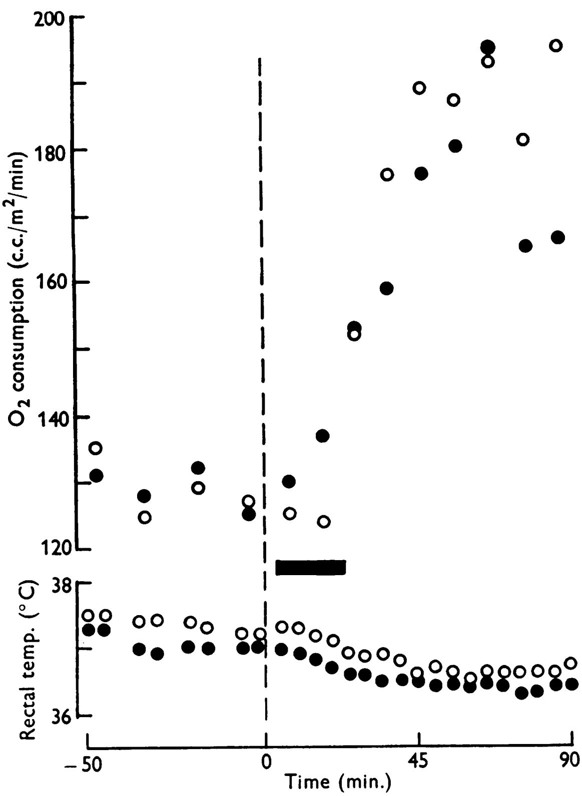

Fig. 5. Oxygen consumption and rectal temperature of subjects lying nude at 20° C room temperature. At zero time 100 mg of hexamethonium bromide was injected intramuscularly. In the experiments indicated by the open circles, sphygmomanometer cuffs applied around the ankles were inflated to 260 mm Hg for a period of 20 min, indicated by the horizontal bar. The solid circles are replots from Fig. 2, and are shown for comparison.

Effects of reduced heat loss from the feet

Wrapping the feet in cotton-wool reduced the rate of fall of temperature in the feet. The changes in the skin temperatures of the other regions were not altered by this procedure. The temperature of the feet at the time of injection of hexamethonium varied greatly, ranging from 29·9 to 34·5° C, but the maximum temperatures reached after injection varied by only $\pm 0{\cdot}3°$ C from the mean of 35·2° C. The rise in foot temperature ranged from 0·8 to 5·1° C.

The only alteration in response of rectal temperature was observed in one experiment in which the initial temperature of the feet was high. In this experiment rectal temperature showed a slow decrease of about 0·3° C in 90 min; shivering and increased oxygen consumption did not occur. In the other experiments no significant changes were observed in the pattern of response in rectal temperature, shivering or increased oxygen consumption.

DISCUSSION

Allwood & Burry (1954) have investigated the effects of local temperature on the blood flow to the feet. With plethysmograph temperature of 26° C, which is about the same as the foot temperatures in the present experiments 50 min after the beginning of recordings, these workers obtained values of 0·53–1·3 ml./100 ml. tissue/min. However, the subjects were comfortably warm. Schnapper, Johnson, Tuohy & Freis (1951) obtained similar results from subjects exposed, except for shorts, to a room temperature of about 20° C but with plethysmograph temperatures at 32° C. These observations suggest that the resting blood flow to the feet depends upon general as well as upon local reflex mechanisms. It is possible that with nude subjects exposed to a room temperature of 20° C the blood flow to the feet may be less than those shown in published figures. In the present experiments, the fact that inflation of occlusion cuffs placed around the ankles did not increase the rate of fall of foot temperatures strongly suggests that vasoconstriction is complete early on exposure to cold. Pressure on the nerves during the period of inflation may have resulted in a reduction in the vasomotor tone of the vessels in the feet. This could explain the appearance of 'reactive hyperaemia' after the release of the pressure from the cuffs. It may therefore be assumed that loss of body heat through the feet was very small during the control periods.

The appearance of shivering after about 2 hr exposure to moderate cold is a common observation. In the present control experiments, shivering appeared without any change in rectal temperature. This suggests that the stimulus for shivering was the alteration in skin temperature. The occurrence of shivering after such long delay might depend on the ability of the cold receptors to indicate absolute temperature as well as the rate of temperature change (Hensel, 1952), and also the summation of impulses in the temperature regulation centre, as suggested by Carlson (1954). Recent work supports this hypothesis (Spurr, Hutt & Horvath, 1957).

The rapid fall in rectal temperature and the occurrence of shivering after the injection of hexamethonium cannot be explained by assuming increased heat loss from the body subsequent to a rise in skin temperature. The average skin temperature was not altered at the time these changes appeared. Furthermore, reducing the rate of heat loss from the feet did not alter significantly the course of events. The results can, however, be explained by assuming an alteration in the distribution of the heat in the body. The fact that the calculated mean body temperature was not changed by the injection of hexamethonium supports this suggestion. The marked rise in the skin temperature of the feet after hexamethonium indicates that body heat may be shifted to this region. It is known that blood flow to the feet is greatly increased after administration of hexamethonium (Schnaper *et al.* 1951). Blood entering a cold extremity would lose heat to the tissues and return at a lower temperature (Bazett, Love, Newton, Eisenberg, Day & Foster, 1948). This cooled venous blood could produce a drop in rectal temperature and initiate shivering in the manner suggested by Uprus, Gaylor & Carmichael (1935). The possibility that shivering was due to the direct action of hexamethonium is ruled out by the finding that shivering did not occur in the absence of a fall in rectal temperature, or when the rate of fall in rectal temperature was slow.

Lack of information as to the weight of the feet, the specific heat of the tissues of the feet and the exact temperature changes, renders it impossible to calculate accurately the amount of heat necessary to produce the observed average rise of 5·7° C in the skin temperature of the feet. However, by assuming 0·83 kcal/kg/° C for the specific heat, 1·8 kg for the weight of the feet and 5·7° C for the temperature difference, a value of 8·5 kcal is obtained. Removal of this amount of heat from the blood circulating through the feet during the 60 min period of temperature rise can account for the observed fall in rectal temperature. The subsequent steady state with the rectal temperature at a lower level can be explained by assuming that the increased heat production from shivering balances the extra heat lost from: (*a*) increased convection that occurs with shivering and (*b*) the increased surface area for heat dissipation that occurs when the blood re-enters the feet.

Hamilton *et al.* (1954) did not observe shivering or increased oxygen consumption after injection of hexamethonium. In experiments on nude subjects at room temperatures of 26° C Hsieh (unpublished) obtained similar results. The average skin temperatures of the subjects in these experiments were higher and the rectal temperatures fell at a slower rate. The higher average skin temperature could result in an inhibition of shivering (Jung, Doupe & Carmichael, 1937). In these circumstances it is possible that increased heat loss due to reduction in insulation of the body may play an important role in the fall of deep body temperature that occurs after administration of hexamethonium. However, the rise in foot temperature is still considerable (as much as 4° C) and heat lost from the blood to the tissues of this area cannot be ignored.

Hsieh *et al.* (1957) observed a reduction in the oxygen consumption of curarized rats after intravenous injections of hexamethonium and suggested that the drug might act by blocking sympathetic control of chemical regulation of heat production. Oxygen consumption was not reduced by the administration of hexamethonium in the present experiments. Others (Reynolds, Paton, Freeman, Howard & Sherlock, 1953; Hamilton *et al.* 1954) have made similar observations. It may well be that muscular activity in the form of increased muscular tone may still be present even with subjects lying quietly. This would mask any reduction in 'chemical regulation'. Another possibility is that the dose of hexamethonium may have been too small.

SUMMARY

1. The effects of intramuscular injection of hexamethonium bromide on temperature regulation in man have been investigated by following the changes in skin temperature, rectal temperature and oxygen consumption in two male subjects when lying nude in a room maintained at 20° C.

2. Skin temperatures of the head, arms, legs and hands are not altered by the injection of hexamethonium. There are small increases in the temperatures of the trunk and thighs, but these are attributable to the associated shivering in these areas.

3. When sphygmomanometer cuffs placed around the ankles are inflated to about 260 mm Hg soon after the injection of hexamethonium, and the pressure is maintained for 20 min, the above changes do not appear until the pressure is released.

4. The effects of hexamethonium on temperature regulation in the present experiments have been explained on the basis of increased blood flow through the feet and the thermal state of the feet at the time of the administration of this drug.

The comments of Profs. L. G. Kilborn and L. D. Carlson are gratefully acknowledged. This work was supported in part by a grant from the Research Grants Committee of the University of Hong Kong.

REFERENCES

ALLWOOD, M. J. & BURRY, H. S. (1954). The effect of local temperature on blood flow in the human foot. *J. Physiol.* **124**, 345–357.

BAZETT, H. C., LOVE, L., NEWTON, M., EISENBERG, L., DAY, R. & FORSTER, R., II (1948). Temperature changes in blood flowing in arteries and veins in man. *J. appl. Physiol.* **1**, 3–9.

BURTON, A. C. (1935). Human calorimetry. II. The average temperature of the tissues of the body. *J. Nutr.* **9**, 261–280.

CARLSON, L. D. (1954). The adequate stimulus for shivering. *Proc. Soc. exp. Biol., N.Y.*, **85**, 303–305.

COTTLE, W. H. & CARLSON, L. D. (1956). Regulation of heat production in cold-adapted rats. *Proc. Soc. exp. Biol., N.Y.*, **92**, 845–849.

FINNERTY JR., F. A. & FREIS, E. D. (1950). Experimental and clinical evaluation in man of hexamethonium, a new ganglionic blocking agent. *Circulation*, **2**, 828–836.

GRAYSON, J. & MENDEL, D. (1956). The distribution and regulation of temperature in the rat. *J. Physiol.* **133**, 334–346.

HAMILTON, M., HENLEY, K. S. & MORRISON, B. (1954). Changes in peripheral circulation and body temperature after hexamethonium bromide. *Clin. Sci.* **13**, 225–237.

HARDY, J. D. & DUBOIS, E. F. (1938). The technic of measuring radiation and convection. *J. Nutr.* **15**, 461–475.

HENSEL, H. (1952). Physiologie der Thermoreception. *Ergebn. Physiol.* **47**, 166–368.

HSIEH, A. C. L., CARLSON, L. D. & GRAY, G. (1957). Role of the sympathetic nervous system in the control of chemical regulation of heat production. *Amer. J. Physiol.* **190**, 247–251.

JUNG, R., DOUPE, J. & CARMICHAEL, E. A. (1937). Shivering: a clinical study of the influence of sensation. *Brain*, **60**, 28–38.

MARGARIA, R., MESCHIA, G. & MARRO, F. (1954). Determination of oxygen consumption with Pauling oxygen meter. *J. appl. Physiol.* **6**, 776–780.

REYNOLDS, T. B., PATON, A., FREEMAN, M., HOWARD, F. & SHERLOCK, S. (1953). The effect of hexamethonium bromide on splanchnic blood flow, oxygen consumption and glucose output in man. *J. clin. Invest.* **32**, 793–800.

SCHNAPER, H. W., JOHNSON, R. L., TUOHY, E. B. & FREIS, E. D. (1951). The effect of hexamethonium as compared to procaine or metcaine lumbar block on the blood flow to the foot of normal subjects. *J. clin. Invest.* **30**, 786–791.

SPURR, G. B., HUTT, B. K. & HORVATH, S. M. (1957). Shivering, oxygen consumption and body temperatures in acute exposures of men to two different cold environments. *J. appl. Physiol.* **11**, 58–64.

UPRUS, V., GAYLOR, G. B. & CARMICHAEL, E. A. (1935). Shivering: a clinical study with especial references to the afferent and efferent pathways. *Brain*, **58**, 220–232.